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Oxidation of 4-arylphenol trimethylsilyl ethers to *p*-arylquinols using hypervalent iodine(III) reagents

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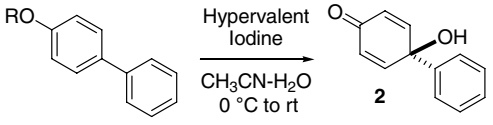
Abstract—An efficient synthesis of *p*-arylquinols by the oxidation of 4-arylphenol trimethylsilyl ethers with phenyliodine(III) diacetate (PIDA) is reported. This protocol greatly improved the yield of *p*-quinol by minimizing oligomer side products compared to the oxidation of free phenol with hypervalent iodine(III) reagents. The innocuity of phenyliodine(III) diacetate associated with the mild conditions make the method highly competitive over metal-mediated oxidation reactions. The proposed reaction mechanism is discussed and compared to the generally accepted mechanism of 4-substituted phenols to explain the yield improvement.

p-Quinols are important skeletons found in many biologically active natural products[1] as well as being important intermediate skeletons in multi-steps synthesis.[2] On the other hand, Westwell et al. reported *p*-quinols based antitumor agents, which represent structurally new and original skeletons.[3] Westwell et al. prepared *p*-quinols by dearomatization of phenols using Phenyliodine(III) bis-trifluoroacetate (PIFA) as the oxidating agent. However, yields of the required *p*-quinols were low due to the generation of radical species that might lead to unwanted by-products. Consequently, although attractive due to the non toxic nature of hypervalent iodine(III) reagents and the simplicity of the method,[4] this approach is often hampered by limited yields as a result of competitive *ortho* oxidation and/or oligomerization processes. As part of a program directed at the discovery of new anticancer agents, we were interested in the incorporation of *p*-quinol skeletons in our own structures.[5] For this purpose, we have re-examined the hypervalent iodine(III) mediated oxidation of phenol derivatives.

We first selected 4-phenyl phenol **1** as a model substrate in the presence of water as nucleophile (Table 1). Despite numerous attempts, we were unable to isolate the corresponding *p*-arylquinol **2** in higher yield than 43% (entry 1). We observed extensive oligomerization dramatically decreasing the yields of isolated *p*-arylquinol **2**. Phenyliodine(III) bis-trifluoroacetate (PIFA) has a deleterious effect on the yield causing much more oligomerization than phenyliodine(III) diacetate (PIDA) (entry 1 vs 2). We believe that the side products are formed as a result of the formation of a highly reactive phenoxonium ion (vide infra). With the intention to minimize this intermediate, we envisaged the oxidation of the corresponding protected phenol. Although oxidative dealkylation has been reported for the formation of quinones,[6] phenol methyl ether **3** was found to be mostly

Table 1. Study of phenol protecting group



Entry	*R*	Substrate	Hypervalent iodine	Yield (%)
1	H	**1**	$PhI(OAc)_2$	43
2	H	**1**	$PhI(OCOCF_3)_2$	17
3	CH_3	**3**	$PhI(OAc)_2$	Trace
4	CH_3	**3**	$PhI(OCOCF_3)_2$	Trace
5	CH_3SO_2	**4**	$PhI(OAc)_2$	0
6	CH_3SO_2	**4**	$PhI(OCOCF_3)_2$	0
7	$\mathbf{Si(CH_3)_3}$	**5**	$\mathbf{PhI(OAc)_2}$	**82**
8	$Si(CH_3)_3$	**5**	$PhI(OCOCF_3)_2$	35

Keywords: *p*-Arylquinols; Hypervalent iodine(III) reagents; Oxidation; Dearomatization.
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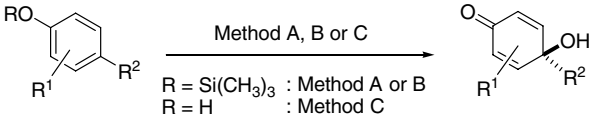
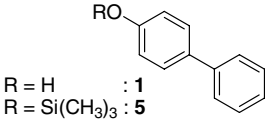
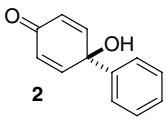
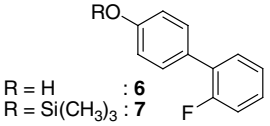
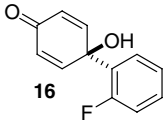
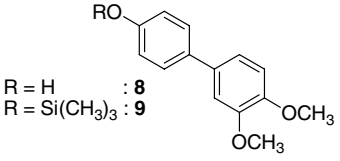
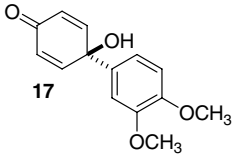
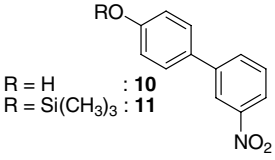
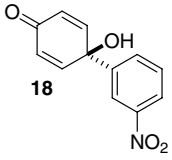
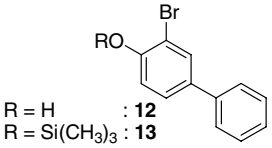
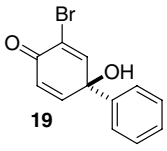
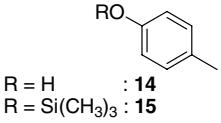
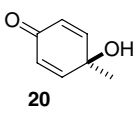
unreactive in our studies (entries 3 and 4). Mesyl protecting group also inhibited the oxidative dearomatization (entries 5 and 6). Then, we studied the reactivity of trimethylsilyl ether **5**.[7] Although the oxidation of **5** with PIFA gave disappointing low yields causing extensive oligomerization (entry 8), we found that the use of PIDA led to the desired *p*-arylquinol **2** in an excellent yield and purity (entry 7). These results are of importance since trimethylsilyl ethers are easily accessible by a simple heating of the free phenols with HMDS in the presence of pyridine.[8]

We then examined the impact of the structure of the 4-arylphenol derivatives on the reaction outcome (Table 2). With a variety of phenols or their trimethylsilyl ether derivatives in hand, we studied the hypervalent iodine(III)-mediated dearomatization, in the presence of water as nucleophile, with three different methods: (A) oxidation of 4-arylphenol trimethylsilyl ethers with PIDA, (B) oxidation of 4-arylphenol trimethylsilyl ethers with PIFA and (C) oxidation of 4-arylphenols with PIDA. As expected, method A (e.g., oxidation of 4-arylphenol trimethylsilyl ethers with PIDA) proved to be the most efficient way to obtain *p*-arylquinols as the only identifiable product by TLC. In most cases, we found a spectacular positive effect for the yield when the oxidation was carried out on protected phenols as illustrated by the most impressive one in entry 5. While

Table 2. Screening of 4-arylphenol derivatives oxidation



Entry	Substrate	Product	Yield (%) Method[a]		
			A	B	C
1	 R = H : **1** R = Si(CH3)3 : **5**	 **2**	**82**	35	43
2	 R = H : **6** R = Si(CH3)3 : **7**	 **16**	**76**	56	38
3	 R = H : **8** R = Si(CH3)3 : **9**	 **17**	**0**	0	0
4	 R = H : **10** R = Si(CH3)3 : **11**	 **18**	**78**	70	49
5	 R = H : **12** R = Si(CH3)3 : **13**	 **19**	**70**	59	0
6	 R = H : **14** R = Si(CH3)3 : **15**	 **20**	**66**	62	44

[a] Method A: oxidation of 4-arylphenol trimethylsilyl ethers with PIDA; Method B: oxidation of 4-arylphenol trimethylsilyl ethers with PIFA; Method C: oxidation of 4-arylphenol with PIDA.